Selective Serotonin Reuptake Inhibitors and Congenital Heart Anomalies:

Comparative Cohort Studies of Women Treated Before and During Pregnancy and Their Children

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ABSTRACT

Background: Large databases and population registers are increasingly used to examine adverse birth outcomes, congenital heart anomalies, in particular, following antidepressant exposures in pregnancy. Yet many studies have failed to account for other characteristics of the women who were prescribed antidepressants.

Objective: To examine the characteristics of women who are prescribed selective serotonin reuptake inhibitors (SSRIs) in pregnancy and women who are not, associations between SSRIs prescribed in pregnancy and congenital heart anomalies, and the association between social and lifestyle characteristics of pregnant women and congenital heart anomalies.

Method: Using data from The Health Improvement Network primary care database in the United Kingdom between January 1, 1990, and January 31, 2011, we set up a comparative study including 4 cohorts of children of women with and without different antidepressant exposures before and during pregnancy. 5,154 women were receiving SSRIs before pregnancy, 2,776 were receiving SSRIs during pregnancy, 992 were receiving other antidepressants during pregnancy, and 200,213 were receiving no antidepressants before or during pregnancy. Our primary outcome was congenital heart anomalies.

Results: Less than 1% of children had a record of congenital heart anomalies within 5 years of birth, and there were no significant differences related to antidepressant exposure in pregnancy (women not prescribed antidepressants versus women prescribed SSRIs in first trimester: odds ratio [OR] = 1.00; 95% CI, 0.65–1.52); however, independent of antidepressant prescribing, diabetes (OR = 2.23; 95% CI, 1.79–2.77), increasing age (OR = 1.01; 95% CI, 1.00–1.02), alcohol problem (OR = 2.58; 95% CI, 1.55–4.29, illicit drug problems (OR = 1.89; 95% CI, 1.09–3.25), and obesity (OR = 1.38; 95% CI, 1.13–1.69) were associated with an increased risk of having a child with congenital heart anomalies.

Conclusions: There was no difference in congenital heart anomalies in children born to women with different antidepressant prescribing exposure status. However, we confirmed an increased risk of congenital heart anomalies in children of older women and in children of women with diabetes, a body mass index above 30 kg/m^2, and a history of alcohol and illicit drug problems independent of the prescription of antidepressants. Future research in this field must account for these characteristics. On the basis of existing evidence, advising women to stop antidepressant treatment in pregnancy may be counterproductive.

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The tragic teratogenic effects of thalidomide in the early 1960s have heightened awareness of the potential risks associated with medications taken in pregnancy. In recent years, particular focus has been on adverse effects of selective serotonin reuptake inhibitors (SSRIs) in pregnancy (eg, references 1–9), perhaps because SSRIs are one of the most commonly prescribed medications in pregnancy.[10–12] Research on SSRIs in pregnancy is often based on large database or population registry studies and has covered many different outcomes such as persistent pulmonary hypertension,[13,14] autism,[15] and congenital malformations, especially cardiac malformations,[3–7,16] but with conflicting results. The biological mechanism for congenital cardiac anomalies in a fetus exposed to SSRIs is not well understood. In addition to acting as a neurotransmitter involved in signaling between neurons, serotonin also acts as a signaling molecule during embryogenesis affecting cell proliferation, migration, death, and differentiation. Thus, serotonin may be influencing heart development as it may act as an important signaling neurotransmitter.[17]

Although the strength of population registry study data is that they provide large samples of pregnant women, often research has failed to adequately account for potential confounding factors including diabetes, obesity, illicit drug use, other psychotropic medication use, and alcohol intake.[18] Further, the comparison groups in many of these studies are samples of pregnant women in the general population, which make it difficult to disentangle the adverse effects of SSRIs from those associated with the underlying illnesses.[18,19] Only a few studies compare pregnancy outcomes in women with depression who have received antidepressant treatment against those not prescribed an antidepressant,[19,20] and the decision whether to stop or continue antidepressant treatment in pregnancy remains a dilemma for both women and health care providers. Thus, the potential risks of antidepressant treatments need to be weighed against the effects of untreated psychiatric disorders in pregnancy.[21]

We examined the association between SSRIs prescribed in pregnancy and congenital heart

Clinical Points

- Women continue to receive conflicting messages on whether they should continue taking antidepressants during pregnancy, and many women may discontinue antidepressants in pregnancy because they fear adverse effects on the unborn child.
- Our research adds to the ongoing debate on whether these drugs cause congenital heart anomalies, and we found no evidence of any such effect. On the other hand, we found that other factors such as increasing age, diabetes, and alcohol and illicit drug use were important risk factors of congenital heart anomalies.
- Health care professionals should counsel women on the risks contributing to congenital heart anomalies in children (ie, age, diabetes, alcohol problems, and illicit drug use) rather than advising withdrawal of antidepressant medication during pregnancy.

anomalies, which are among the most common congenital malformations, in children using data from The Health Improvement Network, a primary care database of the United Kingdom. We sought to gain further insight into the risks of congenital heart anomalies in children and the social and lifestyle characteristics of women taking SSRIs by using a comparative design that included women with different exposure status to antidepressants.

Our specific objectives were to examine

1. characteristics of women who were prescribed SSRIs in pregnancy and women who were not,
2. associations between SSRIs prescribed in pregnancy and congenital heart anomalies, and
3. association between social and lifestyle characteristics of pregnant women and congenital heart anomalies in their children.

METHOD

We used data from The Health Improvement Network primary care database (http://csdmruk.cegedim.com), one of the largest primary care databases in the United Kingdom that provide longitudinal health records. The Health Improvement Network currently holds data from more than 560 practices, including over 11 million patients, and is roughly representative of the UK population.[22] Over 98% of the UK population are registered with a general practitioner (family doctor).[23] Diagnoses and symptoms are recorded by practice staff using Read codes, a hierarchical coding system used in UK primary care.[24] In addition, the database holds individual patient-level information about year of birth, date of registration, and death or transfer out of the practice. Social deprivation is recorded for each individual by quintiles of Townsend scores. The scores are based on a patient's postcode and linkage to population census data for 2001 for approximately 150 households in a postal area. The score is a combined measure of household owner-occupation, car ownership, overcrowding, and unemployment.

Individuals from the same family/household registered with the same practice are linked by a household identifier. While antenatal care is often shared between general practice and midwives, the general practitioner remains responsible for women's general medical care during pregnancy including the prescribing of medications.

Study Design: Comparative Cohort Studies

We identified all available mother and child pairs from The Health Improvement Network by household identifier, delivery information, and date of birth. The mother-child pairs were included in 1 of 4 cohorts (see Exposures and Cohorts section) if the mother was registered with a general practice after January 1, 1990, for at least 6 months before start of the last menstrual period and if the mother and child were still registered at least 6 months after the delivery and before January 31, 2011. Only live singleton births were considered in the analysis, and the length of pregnancy was determined from information on the gestational age of the baby at birth, ultrasound scans, information on the last menstrual period, and associated free text. If there was no information on the length of the pregnancy, it was assumed to be 280 days from the start of the last menstrual period to delivery.

Exposures and Cohorts

As the database does not hold a direct measure of whether women actually take prescribed medication, we considered women to be on antidepressants only if 2 or more prescriptions were recorded and the gaps between prescriptions were less than 4 months. We included women who received antidepressants at or above the standard recommended British National Formulary level for the treatment of depression and anxiety disorders and excluded women prescribed amitriptyline at weaker strengths (eg, 10 mg), which may be used for other indications (eg, migraine prophylaxis and in the treatment of neuropathic pain). In the United Kingdom, general practitioners (family doctors) use the British National Formulary as their guidance for prescribing (www.medicinescomplete.com/about/publications.htm).

The cohorts included mother-child pairs of women who (1) received SSRI prescriptions between 6 and 2 months before pregnancy, but not during pregnancy; (2) received at least 1 SSRI prescription between 6 and 14 weeks (inclusive) after the start of the last menstrual period, which is the critical period of the development of the heart and other organs[25]; (3) were prescribed other antidepressants in the same period as cohort 2; and (4) did not receive antidepressants at any time during the 6 months before or during pregnancy.

Women who were prescribed antidepressants in the period between 1 month and up to 6 weeks after the start of the last menstrual period but not after 6 weeks of pregnancy were excluded from all cohorts. We recognized that some of these women may have been exposed to antidepressants in the critical period of the development of the heart and other organs, but many may also have discontinued medication.

Outcome

The primary outcome measure was congenital heart anomalies up to 5 years of age (see eAppendix 1) as noted in the child's medical records.

Characteristics of the Women and Children

We identified characteristics that potentially affected the association between antidepressants and congenital heart anomalies. These included maternal age (at start of pregnancy), obesity, smoking, social deprivation, other psychotropic medication use (antipsychotics, antiepileptic drugs, hypnotics, and anxiolytics), alcohol problems (defined by records of alcoholism or alcohol consumption of more than 35 units per week), illicit drug use (defined by records of illicit drug use or treatment thereof), preterm birth (defined by a record in the mother's or child's notes), and diabetes (defined by records that indicate that the individual has diabetes or clinical management codes for diabetes, eg, diabetes annual check, hemoglobin A_{1c} diabetic control). Alcohol problems, illicit drug use, and smoking are not recorded on a regular basis in UK primary care; hence, data were extracted from the women's electronic health care records up to 3 years prior to the start of and during pregnancy. Women were considered obese if they had a record of body mass index above 30 kg/m^2 or a Read code indicating obesity in the period 12 months to 1 month before the start of the last menstrual period. Women were considered to receive other psychotropic medications in pregnancy if they received at least 1 prescription within 4 months and at least 1 of these prescriptions between 6 and 14 weeks (inclusive) after the start of the last menstrual period. Children were considered to be born prematurely if the length of pregnancy was estimated to be less than 37 weeks.

In total, we identified 210 children with Down syndrome. Because Down syndrome is a known and strong risk factor for congenital heart anomalies that are associated with a specific gene (trisomy 21) rather than environmental exposure, these mother-child pairs were excluded from the study.

Analyses

We initially carried out descriptive analyses on the women in each of the 4 cohorts, which included demographic details, the types of antidepressants prescribed, the presence of comorbid problems (eg, diabetes, alcohol and illicit drug use), and the prevalence of congenital heart anomalies. Continuous variables (eg, age) were described in term of medians and interquartile ranges and proportional data (eg, numbers with diabetes) as percentages. Comparisons were then made between women receiving at least 1 SSRI prescription between 6 and 14 weeks (inclusive) after the start of the last menstrual period (cohort 2) and the following:

1. those with SSRI prescriptions between 6 and 2 months before pregnancy, but not during pregnancy (cohort 1),
2. those prescribed other antidepressants in the same period (cohort 3), and
3. those that did not receive antidepressants (cohort 4).

We used logistic regression to estimate the unadjusted and adjusted (age, level of deprivation, smoking status, known history of alcohol and/or drug use, receipt of prescription for antipsychotics and/or anxiolytics, and known history of diabetes) odds ratios (ORs) with 95% confidence intervals for congenital heart anomalies. We identified children who were born preterm, but did not include this information in the models as prematurity may potentially be on the causal pathway between antidepressant prescription in pregnancy and congenital heart anomalies.

All analyses were performed in Stata 12.1 (StataCorp).

Ethics

The scheme for The Health Improvement Network to obtain and provide anonymous patient data to researchers was approved by the National Health Service South-East Multicenter Research Ethics Committee in 2002, and scientific approval for this study was obtained from the Cegedim Strategic Data Medical Research Scientific Review Committee (reference no. 13-065).

RESULTS

In total, 209,135 pairs of women and children were included in the study. The predominantly prescribed SSRIs were fluoxetine and citalopram, followed by paroxetine, sertraline, and escitalopram (Table 1). These constituted more than 99% of the SSRIs prescribed. Venlafaxine, amitriptyline, dosulepin (previously called dothiepin), lofepramine, and clomipramine were the 5 most commonly prescribed non-SSRI antidepressants.

The median cohort ages were 28 to 31 years, with those who received antidepressants in pregnancy (cohorts 2 and 3) being slightly older than those not receiving antidepressants in pregnancy (cohorts 1 and 4) (Table 1). In general, women who were prescribed antidepressants both before and during pregnancy (cohorts 1, 2, and 3) shared many of the same characteristics. Thus, of those who were prescribed antidepressants, 45% to 47% were from areas of greatest deprivation (Townsend quintiles 4 and 5) compared to 34% of the women not prescribed the drugs (Table 1). Around a third of the women prescribed antidepressants before or during pregnancy were smokers, and 8.3% to 10.7% were obese; while in the cohort not prescribed antidepressants (cohort 4), the figures were 19.7% for smoking and 4.9% for obesity (Table 1). The proportion of women with entries in their notes of alcohol problems and illicit drug use were less than 0.5% in women not prescribed antidepressants (cohort 4) (Table 1). In contrast, 4.3% to 6.5% of the women prescribed SSRIs or other antidepressants in pregnancy had records of illicit drug use and 2.3% to 4.1%, records of alcohol problems (Table 1). Around 5% of the women prescribed any antidepressants in pregnancy (cohorts 2 and 3) had diabetes, nearly double that of the women not prescribed these drugs (Table 1). In general, few women

Table 1. Characteristics of Women and Their Children in the 4 Cohorts

Characteristic	Cohort 1[a]	2[b]	3[c]	4[d]
N	5,154	2,776	992	200,213
Median age, y (IQR)	28 (24, 33)	30 (26, 34)	31 (27, 35)	29 (25, 33)
Townsend, n (%)				
1	949 (18.4)	462 (16.6)	154 (15.5)	49,602 (24.8)
2	854 (16.6)	440 (15.9)	185 (18.6)	40,526 (20.2)
3	1,011 (19.6)	609 (21.9)	191 (19.3)	41,931 (20.9)
4	1,268 (24.6)	672 (24.2)	228 (23.0)	39,429 (19.7)
5	1,072 (20.8)	593 (21.4)	234 (23.6)	28,725 (14.3)
SSRIs (5 most common), n (%)				
Fluoxetine	2,133 (41.4)	1,048 (37.8)		
Citalopram	1,654 (32.1)	911 (32.8)		
Paroxetine	582 (11.3)	390 (14.0)		
Sertraline	523 (10.3)	326 (11.7)		
Escitalopram	254 (4.9)	97 (3.5)		
Other antidepressants (5 most common), n (%)				
Venlafaxine			218 (22.0)	
Amitriptyline			195 (19.7)	
Dosulepin (dothiepin)			178 (17.9)	
Lofepramine			90 (9.1)	
Clomipramine			55 (5.5)	
Diabetics, n (%)	178 (3.5)	127 (4.6)	48 (4.8)	5,188 (2.6)
Alcohol problems, n (%)	80 (1.6)	114 (4.1)	23 (2.3)	735 (0.4)
Illicit drug use, n (%)	83 (1.6)	118 (4.3)	64 (6.5)	867 (0.4)
Smoking, n (%)	1,625 (31.5)	984 (35.4)	339 (34.2)	39,358 (19.7)
Obese, n (%)	426 (8.3)	296 (10.7)	83 (8.4)	9,782 (4.9)
Antipsychotics, n (%)	1 (0.02)	49 (1.8)	54 (5.4)	62 (0.03)
Anxiolytics, n (%)	8 (0.2)	52 (1.9)	60 (6.0)	83 (0.04)
Hypnotics, n (%)	6 (0.1)	62 (2.2)	44 (4.4)	61 (0.03)
Antiepileptic drugs, n (%)	15 (0.3)	36 (1.3)	30 (3.0)	697 (0.3)
Children				
Males, n (%)	2,618 (50.8)	1,415 (51.0)	493 (49.7)	102,923 (51.4)
Born before 37 weeks, n (%)	442 (8.6)	297 (10.7)	153 (15.4)	14,943 (7.5)
Children with congenital heart anomalies, n (%)	46 (0.9)	23 (0.8)	6 (0.6)	1,452 (0.7)
Time followed up after birth, median months (IQR)	51 (24,60)	39 (19, 60)	55 (26, 60)	57 (27, 60)
Time to first record of congenital heart anomalies, median months (IQR)	3 (1, 5)	1 (0, 3)	1(0, 16)	2 (1, 6)

[a]Cohort 1: Received SSRI prescriptions between 6 and 2 months before pregnancy start.
[b]Cohort 2: Received SSRI prescriptions between 6 and 14 weeks after the start of the last menstrual period (inclusive) of pregnancy.
[c]Cohort 3: Prescribed non-SSRI antidepressants in the same period as cohort 2.
[d]Cohort 4: Did not receive antidepressants at any time during the 6 months before or during pregnancy.
Abbreviations: IQR = interquartile range, SSRI = selective serotonin reuptake inhibitor.

received other psychotropic medications in pregnancy, but, of those prescribed antidepressants, 1.3% to 6.0% were also prescribed other psychotropic medication (Table 1).

In total, 1,527 children had records indicating a congenital heart anomaly. The absolute risks of congenital heart anomalies were less than 1% in all 4 cohorts (Table 1). Most of these were recorded within months of birth (Table 1), and the majority, 1,306 (86%), had their first entry of a congenital heart anomaly within the first year of life. Some children had more than 1 entry in their notes of congenital heart anomalies. The predominant types of anomaly entries were ventricular septal defects (792 children, 52%) and atrial septal defects (214 children, 14%). The proportion of children with congenital heart anomalies according to the specific SSRI prescribed varied slightly, but was nonsignificant for the 4 most commonly prescribed SSRIs ($\chi^2_3 = 1.45$, $P = .694$). A large proportion of the children born to women prescribed antidepressants in pregnancy were born before 37 weeks of gestation. In the case of non-SSRI antidepressants (cohort 3), 15% were born before 37 weeks, which was double the number of children born to women without antidepressant prescriptions (cohort 4) (Table 1).

Women who were prescribed SSRIs in pregnancy (cohort 2) were found not to be at greater risk of giving birth to a child with a congenital heart anomaly than other women (Table 2). Neither did women who were prescribed non-SSRI antidepressants in pregnancy (cohort 3) experience a higher risk compared to women in the other cohorts (results not shown). The finding persisted after adjustment for sociodemographic status, lifestyle characteristics, and other psychotropic medication (Table 2). Notably, there was a strong association between congenital heart anomalies in children of women with an entry of alcohol problems and/or illicit drug use in their electronic health records in the comparison between cohorts 2 and 4 (Table 2). Likewise, increasing maternal age, obesity, and diabetes were associated with an increased risk of congenital heart anomalies (Table 2).

Table 2. Associations Between SSRI Prescription in Early Pregnancy and Congenital Heart Anomalies

Comparison	Unadjusted Odds Ratios (95% CI)	Adjusted Odds Ratios[a] (95% CI)	*P* Values[a]
Cohort 2[b] versus 1[c]	0.93 (0.56–1.53)	0.82 (0.48–1.38)	.45
Age		1.00 (0.96–1.04)	.94
Alcohol		2.28 (0.78–6.72)	.11
Antipsychotics		1.39 (0.16–12.01)	.77
Anxiolytics		1.39 (0.19–12.67)	.69
Diabetes		**3.49 (1.62–7.50)**	**<.01**
Illicit drug		**2.76 (1.04–7.27)**	**.04**
Obesity		1.17 (0.55–2.50)	.68
Smoker		0.92 (0.54–1.55)	.74
Townsend deprivation[d]			
1		1	.13
2		1.69 (0.73–3.93)	
3		1.42 (0.61–3.27)	
4		0.76 (0.30–1.89)	
5		1.88 (0.84–4.24)	
Cohort 2[b] versus 3[e]	1.37 (0.56–3.38)	1.48 (0.58–3.73)	.41
Age		1.06 (0.99–1.14)	.08
Alcohol		**4.45 (1.38–14.35)**	**.01**
Antipsychotics		2.12 (0.45–10.09)	.35
Anxiolytics		0.75 (0.09–6.27)	.79
Diabetes		**3.27 (1.09–9.87)**	**.04**
Illicit drug		2.23 (0.61–8.20)	.23
Obesity		1.24 (0.42–3.68)	.70
Smoker		0.71 (0.30–1.68)	.44
Townsend deprivation[d]			
1		1	.33
2		1.47 (0.46–4.70)	
3		0.86 (0.24–3.03)	
4		0.45 (0.11–1.94)	
5		1.66 (0.52–5.21)	
Cohort 2[b] versus 4[f]	1.14 (0.76–1.73)	1.00 (0.65–1.52)	.98
Age		**1.01 (1.00–1.02)**	**<.01**
Alcohol		**2.58 (1.55–4.29)**	**<.01**
Antipsychotics		0.92 (0.12–6.73)	.93
Anxiolytics		0.69 (0.09–5.05)	.71
Diabetes		**2.23 (1.79–2.77)**	**<.01**
Illicit drug		**1.89 (1.09–3.25)**	**.02**
Obesity		**1.38 (1.13–1.69)**	**<.01**
Smoker		0.96 (0.84–1.10)	.59
Townsend deprivation[d]			
1		1	.75
2		1.09 (0.94–1.28)	
3		1.09 (0.94–1.27)	
4		1.07 (0.91–1.26)	
5		1.08 (0.91–1.29)	

[a]Bold indicates significance. *P* values refer to the results of the adjusted analysis.
[b]Cohort 2: Received SSRI prescriptions between 6 and 14 weeks after the start of the last menstrual period (inclusive) of pregnancy.
[c]Cohort 1: Received SSRI prescriptions between 6 and 2 months before pregnancy start.
[d]The effects of social deprivation (quintiles of Townsend scores) were tested by Wald tests.
[e]Cohort 3: Prescribed non-SSRI antidepressants in the same period as cohort 2.
[f]Cohort 4: Did not receive antidepressants at any time during the 6 months before or during pregnancy.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

DISCUSSION

Less than 1% of the children in this study had a record of congenital heart anomalies within 5 years of birth, and there were no significant differences in the rates of congenital heart anomalies related to antidepressant prescription status. However, independent of antidepressant prescribing, we found that diabetes, increasing age, records of alcohol problems and illicit drug use, and obesity were associated with an increased risk of the birth of a child with congenital heart anomalies. There were substantial differences in sociodemographics and lifestyle characteristics of the women, in particular between those taking antidepressants versus women from the general population. Although, the absolute number of individuals with entries of alcohol problems and illicit drug use was small, such use was up to 16 times more common among women who continued antidepressants in pregnancy.

Strengths and Limitations

One of the strengths of this study is its comparative nature, including women with different exposure status to antidepressants before and during pregnancy. Many previous studies only used a group of women who were not depressed and were without prescribed antidepressants as the comparison group. Other studies have sought to examine the impact of depression on its own on adverse birth outcomes, eg, references 16, 19, and 26. However, in the United Kingdom, depression is not consistently recorded in women's primary care electronic records, and the use of Read codes for recording depression has changed substantially over the last decades.[27] Therefore, we decided not to attempt to identify and compare a group of women with depression without antidepressant treatment in pregnancy to women who were prescribed antidepressants. Antidepressants are also prescribed for indications other than depression such as various anxiety disorders, eg, panic disorders, obsessive-compulsive disorders, and generalized anxiety disorders; SSRIs such as fluoxetine can be prescribed for bulimia nervosa.

In bespoke pregnancy cohort studies, data are often collected at specific time points, and all women are asked the same questions. In contrast, primary care databases include clinical records from when women visited their general practitioner, and records are made when they are relevant to clinical practice. Therefore, we had to take a pragmatic approach when we extracted data on, for example, smoking, alcohol problems, and illicit drug use and used information recorded up to 3 years prior to the start of or during pregnancy. This means that some women may not have had an alcohol problem, smoked, or used illicit drugs during pregnancy, and such misclassification may dilute the estimated associations observed between these exposures and congenital heart anomalies. Also, we are aware that primary care databases do not have information on dispensing or compliance to medication. Therefore, to minimize exposure misclassification, we used repeat prescription as a marker of women likely to have used some of the prescribed medication. Yet, actual antidepressant exposure is very difficult to ascertain even from bespoke cohorts and studies based on dispensing data. On the other hand, a study based on clinical records may be subject to ascertainment bias of the outcome. Thus, women prescribed antidepressants may be more likely to have their children subjected to cardiac ultrasound examination leading to diagnoses of more

clinically insignificant congenital heart anomalies. Finally, it is possible that women with more severe psychiatric disorders were more likely to continue antidepressants in pregnancy. However, it is difficult to know if that would have any direct impact on our results other than through the variables already included in the study.

It is possible that spontaneous abortions, still births, and neonatal deaths occur more often in women who are depressed and/or prescribed antidepressants, and consideration of live birth outcomes may lead to a potential bias. However, a recent study that examined pregnant women who were issued an SSRI prescription by pharmacists did not find any such associations,[8] and a recent systematic review did not find any association with antidepressant medication exposure and spontaneous abortion (OR = 1.47; 95% CI, 0.99–2.17; $P = .055$).[1]

Discussion of Our Findings in Relation to Existing Literature

Two Scandinavian studies[4,5] also failed to find an overall association between pharmacy redemption of SSRIs in the first trimester of pregnancy and congenital malformations; a similar conclusion was made in 3 recent UK studies[7,16,28] also based on primary care records and a large American study[26] based on health insurance claims data after confounding adjustments were made. However, 3 of these studies[4,5,16] performed extensive subgroup analyses and observed an increased risk of specific congenital heart anomalies associated with specific SSRIs. These findings may be subject to type 1 errors (identification of positive associations when there are none).[16,18] Another Scandinavian study[20] identified an association between congenital heart anomalies and the redemption of antidepressants in the first trimester when compared to women not issued the drugs, but a similar association was found in children of women who paused treatment in pregnancy, suggesting that the former association was confounded by indication.

Two recent systematic reviews[2,3] of the associations between SSRI treatment in pregnancy identified associations between paroxetine and specific congenital heart anomalies. However, most studies were unable to account for confounding by characteristics of the women, and Grigoriadis and colleagues[2] suggest that these marginal findings may be the result of residual confounding. Malm et al[5] and Reis and Källén[29] raised the issue of alcohol exposure in pregnancy, but in the absence of alcohol intake data, were unable to adjust for it in their analysis. However, Malm et al[5] noted that fetal alcohol spectrum disorders were 10 times more common in the SSRI-exposed offspring. Reis and Källén[29] also noted that women who were prescribed antidepressants in pregnancy were characterized by higher age, were more often smokers, and had a high body mass index.[29] Similar findings were observed in a Danish cross-sectional survey[30] that examined the associations between alcohol, smoking, and body mass index and the dispensing of SSRIs in women of childbearing ages.

Our findings that a relatively high proportion of women treated with antidepressants in pregnancy (cohort 2 and 3) gave birth to a child before 37 weeks of gestation is consistent with previous research. A recent systematic review[31] suggested increased risk of preterm birth in women taking antidepressants during pregnancy (pooled adjusted ORs [95% CI] were 1.53 [1.40–1.66] for antidepressant use at any time and 1.96 [1.62–2.38] for third trimester use). However, these findings may be due to residual confounding.[31]

The uncertainty around the adverse effects of prescribed medication in pregnancy leaves many women in a dilemma whether to continue psychotropic medication in pregnancy.[32] Most women discontinue antidepressants either before or within weeks of becoming pregnant.[33,34] While some women may cope well without antidepressant treatment during pregnancy (and potentially benefit from other types of treatments), others may not. While there are a number of case studies illustrating the risks of untreated psychiatric disorders (eg, Jones and Craddock[35]), few studies have been able to quantify the overall risk of relapse or deterioration of mental health.[36,37] Indeed, it is difficult to address whether antidepressants may prevent relapse as those who continue antidepressants in pregnancy may be those who are at highest risk of deteriorating mental and physical health. To advise women to stop antidepressant treatment in pregnancy may prove to be counterproductive and potentially increase the risk of adverse outcomes of pregnancy.[21] Anecdotal evidence suggests that some women who stop antidepressants in pregnancy are likely to "self-medicate" with alcohol and illicit drugs, which should be taken into consideration while weighing the risks and benefits of continuous antidepressant use in pregnancy.

CONCLUSION

The results of our study do not support a general association between SSRIs and congenital heart anomalies. However, we did confirm an increased risk of congenital heart anomalies in children of women of older age, with diabetes, with a history of alcohol problems, with a history of illicit drug problems, and with a body mass index above 30 kg/m^2 independent of the prescription of antidepressants. Future research on the associations between SSRIs and congenital heart anomalies must account for these characteristics. Based on existing evidence, advising women to stop antidepressant treatment in pregnancy may be counterproductive.

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Drug names: citalopram (Celexa and others), clomipramine (Anafranil and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others).

Author contributions: Dr Petersen had the original idea for the study and analyzed the data. She wrote the paper, but all authors made substantial contributions to the interpretation of the data and in the drafting and final approval of the manuscript.

Potential conflicts of interest: **Drs Petersen, Gilbert, Marston,** and **Nazareth** and **Mr Evans** have no conflicts to disclose.

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Database information: For more information about The Health Improvement Network, email info@thin-uk.com.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Selective Serotonin Reuptake Inhibitors and Congenital Heart Anomalies: Comparative Cohort Studies of Women Treated Before and During Pregnancy and Their Children

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List of Supplementary Material for the article

1. **eAppendix 1** The 50 Most Commonly Used “Read” Codes for Congenital Heart Anomalies in Children’s Notes Within the First 5 Years of Life.

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Appendix 1 – The 50 most commonly used Read codes for congenital heart anomalies in children's notes within the first 5 years of life. Please note that some children had more than one record.

Ventricular septal defect
Atrial septal defect NOS
Patent foramen ovale
Tetralogy of Fallot
Coarctation of aorta
Pulmonary stenosis, cause unspecified
Ostium secundum atrial septal defect
Pulmonary infundibular stenosis
Pulmonary stenosis, non-rheumatic
Congenital heart anomaly NOS
Aortic stenosis
Transposition of great vessels
Congenital pulmonary stenosis
Stenosis of pulmonary artery
Congenital aortic valve stenosis
Bicuspid aortic valve
Dextrocardia
Aortic stenosis, non-rheumatic
Pulmonary valve disorders
Pulmonary valve stenosis with insufficiency
Ventricular septal defect in Fallot's tetralogy
Hypoplastic left heart syndrome
Mitral regurgitation
Aortic valve disorders
Ventricular septal defect NOS
Other congenital heart anomalies
Pulmonary valve anomalies
Ebstein's anomaly
Pulmonary artery atresia
Subaortic stenosis
Tricuspid regurgitation, cause unspecified
Cyanotic congenital heart disease NOS
Ventricular septal defect, unspecified
Pulmonary valve disorders NOS
Aortic stenosis alone, cause unspecified
Congenital atresia of the pulmonary valve
Truncus arteriosus
Pulmonary artery anomalies
Aortic arch anomalies
Aortic regurgitation, non-rheumatic
Common atrioventricular-type ventricular septal defect
Other specified heart anomalies
Transposition of coronary artery NEC

Atresia of pulmonary artery with septal defect
Other specified ventricular septal defect
Hypoplasia of heart NOS
Right hypoplastic heart syndrome
Stenosis of unspecified heart valve
Heart septal defects